Chinese herb nephropathy

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In 1994, a 44-year-old woman progressed from normal renal function to advanced renal failure and end-stage renal disease within 8 months. Biopsy revealed extensive interstitial fibrosis with focal lymphocytic infiltration. She received a cadaveric renal transplant in January 1996 and had an uneventful posttransplant course. As a result of a minor motor vehicle accident, the patient had received acupuncture and Chinese herbal medicine for pain relief approximately 5 months before the onset of renal symptoms. After the transplant, analysis of the herbal remedies clearly indicated the presence of aristolochic acid in 2 of the 6 Chinese herbs ingested. Ingestion of aristolochic acid has been linked to a newly defined entity, Chinese herb nephropathy (CHN). This article discusses the history of CHN and its implication in the current case and in other recent similar cases and makes recommendations to avoid future problems caused by unregulated use of herbal medicines. This is the first reported case of CHN in the USA.

A 45-year-old woman with end-stage renal failure was referred for a renal transplant workup in February 1995. She had had normal renal function in November 1993 at age 43 and developed malaise, severe anemia, and advanced renal failure 8 months later. Except for a total hysterectomy for uterine fibroids in 1975, she had been entirely well until she suffered a minor motor vehicle accident in 1993 and developed persistent low back pain. Prior to the accident, she had no history of chronic pain or sustained or intermittent use of nonsteroidal anti-inflammatory drugs or other analgesic medication. She had no personal or family history of renal disease, cardiovascular disease, systemic hypertension, or diabetes mellitus. In early 1994, she began receiving acupuncture and Chinese herbal medicine for pain relief.

Physical examination was unremarkable except for extreme pallor. Preliminary investigation showed a serum creatinine of 6.6 mg/dL, blood urea nitrogen of 55 mg/dL, hemoglobin of 7 g/dL, creatinine clearance of 12.9 mL/min, and 24-hour urine protein of 1.2 g. A renal biopsy was performed at the initial presentation because of uncertainty about the etiology of the rapidly progressive renal failure. The biopsy revealed extensive interstitial fibrosis with focal lymphocytic infiltration; no specific cause was identified. Peritoneal dialysis was initiated. She received a cadaveric renal transplant in January 1996. Her posttransplant course was uneventful, and follow-up creatinine in April 1999 was 1.3 mg/dL.

After transplantation, the patient expressed concern that the Chinese herbal medicine might have caused the renal failure. Samples of the original herbal therapies were sent to Belgium for analysis because recent publications by Belgian physicians suggested an association between renal failure and Chinese herb ingestion. The results of the analysis clearly indicated the presence of aristolochic acid in 2 of the 6 Chinese herbs prescribed, compatible with the diagnosis of Chinese herb nephropathy (CHN).

BACKGROUND

The World Health Organization recognizes that nearly 80% of the world population depends on traditional medicine for primary health care (1). In a society as modern as Hong Kong, up to two thirds of the population choose Chinese herbal medicine as an alternative or complementary source of health care (2).

Various herbal medicines have been studied using modern methods, and some are found to be extremely useful. Aristolochic acid, the component implicated in the present case, has been used in Germany for >25 years as an immunomodulatory drug (3).

J. L. Vanherweghem first described the new entity of CHN (4). He reported 2 patients with rapidly progressive renal failure with similar renal biopsy specimens showing extensive interstitial fibrosis and severe tubular loss most prominent in the outer cortex. These patients were the index cases in a cluster of cases of rapidly progressive renal failure occurring in young women in 1992 to 1993. All the women received a slimming regimen containing Chinese herbs prescribed by the same physician.

Since then, >100 cases have been described in Belgium related to the ingestion of a potentially nephrotoxic ingredient that had been mistakenly substituted for a nontoxic substance (5). Vanherweghem's investigation revealed that in 1990, *Stephenia tetrandra* and *Magnolia officinalis* had replaced pancreas powder, laminaria powder, and fucus extract in the traditional slimming regimen. After the outbreak, thin-layer chromatography was performed on the preparation, and *Aristolochia manshuriensis* rich in aristolochic acid (Radix Aristolochiae fangchi, Guang fangji) was found instead of *Stephenia tetrandra* (Radix Stephaniae

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tetrandrae, Fangji). Aristolochic acid was identified independently by groups from Hong Kong and Belgium from a sample of "pure" *Stephenia* powder distributed in Belgium (2, 6).

Mengs showed that aristolochic acid was nephrotoxic in female Wistar rats, who rapidly developed renal tubular necrosis and renal failure (7). Schmeiser demonstrated the presence of aristolochic acid DNA adducts in the renal tissues of 6 patients with CHN (8).

Cases of severe interstitial nephritis associated with rapidly progressive renal failure have been reported in countries other than Belgium. In 1996, Spanish investigators reported a case of rapidly progressive renal failure in a man who self-treated right upper quadrant pain for 4 years with a homemade infusion containing mint and *Aristolochia pistolochia* (used to treat jaundice in farm animals) (9). In Japan, Tanaka reported 2 cases of CHN from a slimming regimen that contained aristolochic acid but differed from the Belgian formula in that appetite suppressants (fenfluramine, dexfenfluramine, phentermine, and diethylpropion) were not present (10). In 1997, Lord reported the first 2 cases of CHN in the United Kingdom (11). The herbal preparations were from different sources and were prescribed for eczema. High-performance liquid chromatography analysis and mass spectrometry revealed aristolochic acid.

Many cases of CHN developed because of failure to verify the presence of the prescribed herbs. Some of the confusion arose from name similarity (Fangchi vs Fangji) and from lack of precision about the type of MuTong Chinese plant used. MuTong can be derived either from *Aristolochia manshuriensis* or from various species of *Akebia* or *Clematis*. Some patented Chinese medicines contain GuanMuTong, which is derived from *Aristolochia manshuriensis*. Others contain ChuanMuTong from *Clematis armata* and *Clematis montana* and do not contain aristolochic acids.

Morphological findings

Depierreux et al described the pathological findings from the renal biopsies of 33 cases of CHN (12). There was a gradient of intensity from most severe in the outer cortex to less involvement in the inner cortex and medulla. The extent of interstitial fibrosis, tubular atrophy, and complete tubular disappearance was striking.

The interstitium was remarkably hypocellular. There were few lymphocytes infiltrating between tubular epithelial cells. Granulocytes were absent. There was thickening of the walls of interlobular and afferent arterioles. Morphological changes consisted of intimal thickening with fibroblast proliferation and peripheral sclerotic thickening (13). Glomeruli were relatively spared compared with the severity of tubulointerstitial fibrosis. Immunofluorescent staining was essentially negative (12, 13).

Some of the clinical aspects and morphological changes of CHN resemble the changes found in Balkan endemic nephropathy, which may also be caused by toxicity from aristolochic acid (12–14). Mild low-molecular-weight proteinuria, hypertension, severe anemia, and development of uroepithelial atypia are characteristic of both CHN and Balkan endemic nephropathy.

Clinical presentations

To date, 100 women out of a total of 1741 patients who took the adulterated slimming regimen have developed CHN. Reginster reported the clinical presentation and course of slimming regimen–induced CHN in 15 women and compared their course with that of a control group of 15 women with interstitial nephropathies of differing etiology (15). He found that proteinuria was milder; anemia was more severe; and glycosuria, leukocyturia (40%), mild hypertension (80%), and asymmetric kidneys (54%) were more common compared with controls. Creatinine doubling time was significantly shorter in the group of women with CHN. Kabanda found that low-molecular-weight proteinurea was detected before there was a demonstrable decline in glomerular filtration (14).

CHN developed as early as 2 months after exposure to the slimming regimen and as late as 3 years after discontinuation of the drug (15). Generally, the course to end-stage renal disease was subacute and faster than in other tubulointerstitial nephropathies. The 2-year actuarial survival rate without end-stage renal disease was 17% in the CHN group and 74% in the control group (15). Rate of progression was inversely related to the duration of treatment with the Chinese herbs and seemed to be dose related. Those patients who ingested a low dose over many years experienced delayed onset of renal failure and a clinical course like Balkan endemic nephropathy. Reginster postulated that there were both a direct cytotoxicity and a more chronic change involving modification of DNA (15). The presence of aristolochic acid DNA adducts in renal tissue and the association with late development of uroepithelial tumors in patients with CHN support this view. Five out of 12 patients in the original Belgian group developed aortic insufficiency, which was attributed to the presence of fenfluramine in the slimming medicine (16).

Treatment

The rate of progression to end-stage renal disease is so rapid that use of renoprotective agents such as angiotensin-converting enzyme inhibitors or angiotensin blockers to control blood pressure and delay the fibrotic process may not be useful (15). The striking absence of an interstitial infiltrate suggests that steroid treatment would not be efficacious (17). Five patients underwent renal transplantation. There is no evidence that posttransplant immunosuppressive therapies enhanced the development of uroepithelial tumors in the transplanted group or that disease recurred in the transplanted kidney (18).

However, diffuse uroepithelial cell atypia was a common finding in diseased native kidneys removed at the time of transplant. Cosyns et al recommend complete removal of the native kidneys and ureters during or after renal transplantation (18). He found that in all the kidneys removed from the first 10 patients there was moderate multifocal epithelial cell atypia involving the medullary collecting ducts, pelvis, and ureter. Multifocal high-grade transitional cell carcinoma in situ was found in 40% of cases. All of the cells with atypia or actual carcinoma in situ overexpressed p53, a mutated tumor suppressor gene, to varying degrees (18). The development of multifocal, recurrent papillary transitional cell carcinomas of the urothelium and bladder remains the most feared complication of CHN, Balkan endemic nephropathy, and analgesic abuse nephropathy.

Treatment of patients with these disorders requires continued vigilance, frequent urinary cytological evaluation, and scheduled cystoscopy for a lengthy period of time. Some would advocate

bilateral native nephroureterectomy, leaving only the bladder to be monitored.

DISCUSSION

Medicine is often a double-edged sword. It cures and it harms. Clearly, all medications have risk-to-benefit and side effect-to-benefit ratios. It is more difficult to monitor the risks and side effects of naturopathic and herbal remedies that are not usually studied or tested for efficacy or toxicity. These mixtures are not regulated or held to standards in advertising, quality control, or batch-to-batch constancy of ingredients. While alternative medicine is still actively practiced in most modern and sophisticated countries in the world, lack of regulation in the practice of alternative medicine can result in tragedies such as the one cited in this paper.

The occurrence of aristolochic acid–induced renal failure in Belgium is a conundrum. It is estimated that 1741 patients in Belgium took the slimming medication. Only approximately 100 patients with CHN were identified (5). There was no definite correlation between the length of treatment and the occurrence of illness (4). Various investigators have postulated potential explanations including batch-to-batch variability in the amount of aristolochic acid in the imported herbs (8, 18), differences in the duration of exposure (15), unwitting variation in the composition of a remedy (19), individual variation in drug metabolism (6), and gender differences. Men seem to have been protected, although this could be an artifact due to the small number of men taking the slimming medicine.

The herbal preparation contained a cocktail of 10 different Western and Chinese "medicines." Two of the components, fenfluramine (serotonin agonist) and diethylpropion (sympathomimetic), are potent renal vasoconstrictors. Renal ischemia induced by those 2 drugs could have potentiated the nephrotoxic effect of aristolochic acid (20). In a rat model, the sustained preglomerular vasoconstrictive effect of serotonin caused ischemic interstitial nephritis (21). The ischemic injury pattern showed relative sparing of the medulla, similar to the pattern found in CHN. It could be argued that fenfluramine, a potent serotonin agonist, might have caused intense ischemic interstitial nephritis and progression to interstitial fibrosis. Mengs et al reported the rapid development of renal tubular necrosis and renal failure in female Winstar rats fed with aristolochic acid (22), and several other groups in Japan, Belgium, Spain, France, and the United Kingdom have reported renal failure from aristolochic acid in the absence of serotonin agonists (9–11, 20, 23, 24). Aristolochic acid was isolated in 2 of the 6 Chinese herbs prescribed for our patient by the Chinese herbalist. Acetazolamide has been found in some of the herbal preparations and may have enhanced the nephrotoxicity from mild volume contraction and an alkaline urine (19).

This is the first reported case of CHN in the USA. We believe that this form of nephropathy may occur more commonly in the future due to the widespread availability of herbal medicine. Unexplained renal failure together with interstitial fibrosis should alert a physician about the possibility of herbal medicine ingestion.

The sophisticated American consumer would never think of buying a car without fully investigating its reliability, safety, need for repairs, etc. Yet these same consumers are willing to ingest herbal remedies without concern for truth in advertising, efficacy, or safety. Many tragedies have occurred due to unregulated herbal medicine practice (4, 9–11, 20, 23, 24). Various researchers have reported that up to 35% of cases of acute renal failure in parts of Central and Southern Africa were due to native herbal remedies (3, 11). Rapidly progressive interstitial fibrosis due to a homemade remedy for arthritis has been reported (9). Adulteration of Chinese herbal medicine with mefenemic acid has produced acute interstitial nephritis (25). One Chinese herbal medicine, Nan Lien Cui Fong Toukuwan, which is used to treat rheumatism, arthritis, and other pains, was adulterated with >10 different types of Western medicine (26). Even heavy metals were detected. Such contaminants contained in the remedies could lead to nephrotoxicity.

CONCLUSION

Although Chinese herbs in their natural forms, prescribed by a qualified practitioner, are probably safe, they occasionally cause severe adverse reactions. In view of the serious consequences that may arise, the product source, production, and dispensing of naturopathic and homeopathic medicines should be regulated by the Food and Drug Administration to protect the community against the potential hazards. The Food and Drug Administration should require dosing and efficacy testing and should apply the same truth-in-marketing laws required for all other medicines.

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